TAXUS I

Six- and Twelve-Month Results From a Randomized, Double-Blind Trial on a Slow-Release Paclitaxel-Eluting Stent for De Novo Coronary Lesions

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Background—The TAXUS NIRx stent (Boston Scientific Corp) provides local delivery of paclitaxel via a slow-release polymer coating. The TAXUS I trial was the first in-human experience evaluating safety and feasibility of the TAXUS NIRx stent system compared with bare NIR stents (control) (Boston Scientific Corp) for treatment of coronary lesions.

Methods and Results—The TAXUS I trial was a prospective, double-blind, three-center study randomizing 61 patients with de novo or restenotic lesions (≤12 mm) to receive a TAXUS (n=31) versus control (n=30) stent (diameter 3.0 or 3.5 mm). Demographics, lesion characteristics, clinical outcomes were comparable between the groups. The 30-day major adverse cardiac event (MACE) rate was 0% in both groups (P=NS). No stent thromboses were reported at 1, 6, 9, or 12 months. At 12 months, the MACE rate was 3% (1 event) in the TAXUS group and 10% (4 events in 3 patients) in the control group (P=NS). Six-month angiographic restenosis rates were 0% for TAXUS versus 10% for control (P=NS) patients. There were significant improvements in minimal lumen diameter (2.60±0.49 versus 2.19±0.65 mm), diameter stenosis (13.56±11.77 versus 27.23±16.69), and late lumen loss (0.36±0.48 versus 0.71±0.48 mm) in the TAXUS group (all P<0.01). No evidence of edge restenosis was seen in either group. Intravascular ultrasound analysis showed significant improvements in normalized neointimal hyperplasia in the TAXUS (14.8 mm^3) group compared with the control group (21.6 mm^3) (P<0.05).

Conclusions—In this feasibility trial, the TAXUS slow-release stent was well tolerated and showed promise for treatment of coronary lesions, with significant reductions in angiographic and intravascular ultrasound measures of restenosis. (***Circulation.*** **2003;107:38-42.**)

Key Words: stents ■ drugs ■ restenosis ■ coronary disease ■ revascularization

Although the insertion of coronary stents has improved the success of balloon angioplasty for the treatment of coronary artery disease, restenosis after the initial procedure continues to limit its effectiveness. A promising modality to inhibit restenosis is the controlled release of paclitaxel from coronary stents.[1,2] Paclitaxel interferes with microtubule function, affecting mitosis and extracellular secretion, and thereby interrupts the restenotic cascade at multiple levels.[3,4,5] Results from animal models have shown reduced neointimal responses after local paclitaxel delivery to the vessel. A vascular compatible polymer has been developed that provides early, controlled release of paclitaxel.

The purpose of TAXUS I was to provide the first in-human clinical evaluations of a polymer-based paclitaxel-eluting stent in a randomized, multicenter trial comparing the TAXUS NIRx stent with bare metal NIR (control) stents (both from Boston Scientific Corp).

Methods

Device Description

The NIR stent is an uncoated, balloon-expandable stent made of 316LS surgical-grade stainless steel. The TAXUS NIRx stent is the aforementioned stent coated with paclitaxel (1 $\mu g/mm^2$ paclitaxel per unit of stent surface area) in a slow-release formulation of a proprietary polymer (hydrocarbon-based elastomer). Both the coated and uncoated stents were available in 15-mm lengths and either 3.0- or 3.5-mm diameters and were hand-mounted onto the balloon delivery catheter.

Study Population

Between October 2000 and March 2001, 61 patients were randomized to either a single TAXUS paclitaxel-eluting stent or a control (bare metal NIR) stent. The trial was conducted at three German heart centers after the approval of the local ethics committee and informed consent of all subjects had been obtained. Target lesions were single de novo or restenotic coronary lesions. Angiographic inclusion criteria were lesion length ≤12 mm, 50% to 99% diameter stenosis, and vessel diameter between 3.0 mm and 3.5 mm. Patients

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were not eligible for enrollment if they had a history of acute myocardial infarction; a left ventricular ejection fraction <30%; a stroke within the previous 6 months; renal dysfunction, as defined by serum creatinine >1.7 mg/100 mL; or contraindication to aspirin, clopidogrel, or ticlopidine. Target lesions requiring >1 study stent for full coverage were excluded.

Study Administration

This trial was conducted with a strictly double-blinded analysis. To maintain blind packaging, the TAXUS and control stents were indistinguishable by physical and radiographic appearance. The intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) core labs and the Clinical Events Committee were blinded to treatment groups.

Stenting Procedure

Before stent implantation, patients were premedicated with aspirin (>80 mg), clopidogrel (300 mg), and heparin. After predilatation, study stents were deployed according to conventional techniques with IVUS guidance. Postdeployment high-pressure dilatation was at the investigator's discretion. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. One study stent was allowed; use of additional nonstudy stents was at the investigator's discretion. After stent implantation, aspirin (>80 mg/d) was administered for at least 12 months and clopidogrel (75 mg/d) for 6 months.

Follow-Up

Clinical evaluation was scheduled at 1, 6, 9, and 12 months after implantation. Angiographic and IVUS imaging was performed before stent implantation, after the procedure, and at 6 months' follow-up.

Primary End Point

Major adverse cardiac events (MACE), including death from any cause, Q-wave myocardial infarction, target vessel revascularization, and stent thrombosis at 30 days, were defined as the primary end point of this trial. Q-wave myocardial infarction was defined as development of Q waves in ≥2 contiguous leads with postprocedural creatine kinase and isoenzyme (CK-MB) levels elevated above normal. Target vessel revascularization was subclassified as CABG surgery, percutaneous intervention on the target lesions (target lesion revascularization [TLR]) or percutaneous intervention on the nontarget lesion. An independent Clinical Events Committee adjudicated adverse events, including MACE.

Angiographic and IVUS Analysis

Coronary angiograms were obtained in multiple views after intracoronary injection of nitroglycerin. Angiograms and IVUS images were analyzed according to previously published methods by an independent core laboratory (Heart Core, Leiden, the Netherlands). Quantitative coronary angiographic end points included binary restenosis, defined as >50% diameter stenosis; reference vessel diameter (RVD); minimum lumen diameter (MLD); percent diameter stenosis (%DS); late lumen loss; and late loss index. Late lumen loss was measured as the difference between postintervention MLD and MLD at follow-up. RVD, MLD, and %DS were measured before the procedure, after the procedure, and at follow-up.

IVUS images were acquired after the procedure and at the 6-month follow-up visit with the use of automated pull-back after intracoronary administration of nitrates. A computer-based contour detection program was used for automated 3D reconstruction of the segment. Lumen, stent boundaries, and external elastic membrane were detected with a minimum cost algorithm, and volumetric quantification was performed. The total analysis segment included the stented segment as well as the margins 5 mm distal and proximal to the stents.

TABLE 1. Baseline Demographics and Clinical Characteristics

Baseline Demographics	TAXUS*	NIR Control*	P
Male sex	94%	83%	0.255
Age, y	66±6.8	63.8±7.8	0.236
Prior myocardial infarction	26%	30%	0.780
Congestive heart failure	0%	0%	NA
Current hypertension	65%	63%	1.0
Current hypercholesterolemia	81%	81%	1.0
Diabetes	23%	13%	0.507
Smoking history	54%	47%	0.793
Silent ischemia	23%	37%	0.211
CCS angina classification			0.163
1	0	7	
2	61	33	
3	10	20	
4	16	17	
None	13	23	

NA indicates not applicable because of zero value; CCS, Canadian Cardiovascular Society.

*Values are given as percentages (count/sample size) unless indicated otherwise.

Statistical Analysis

Quantitative data are presented as rates or mean value±SD. Probability values are 2-sided from Student's t test for continuous variables and Fisher's exact test for categorical variables. A value of $P<0.05$ was considered significant. The statistical analysis was performed with the aid of commercially available software (SAS Version 6.12).

Results

Demographics

A total of 61 patients were enrolled (TAXUS, n=31; control, n=30). Fifty-nine patients had de novo lesions, and 2 had restenotic lesions. Baseline clinical characteristics and QCA-determined lesion characteristics were similar between the 2 groups (Tables 1 and 2). There was a trend toward a greater use of the TAXUS stent in the left anterior descending artery (LAD) and more severe angina in the control group (P=NS).

Clinical MACE Results

The procedural and technical success rate was 100% for both groups. Nonstudy stents were implanted to optimize results in

TABLE 2. Baseline Lesion Characteristics

Baseline Lesion Characteristics	Taxus	NIR Control	P
Target vessel			0.090
LAD	54.8%	26.7%	
Left circumflex	22.6%	36.7%	
Right coronary artery	22.6%	36.7%	
Type of lesion*			0.200
A	32.3%	13.3%	
B1	38.7%	43.3%	
B2	29.0%	43.3%	
C	0.0%	0.0%	

*Values given as count/sample size.

TABLE 3. MACE and Stent Thrombosis at 1-Year Follow-Up

MACE Event	TAXUS	NIR Control	P
12-Month MACE rate	3% (1/30)	10% (3/30)*	0.612
Death	0	0	NA
Q-wave myocardial infarction	0	0	NA
Percutaneous coronary intervention—target vessel	3%	10%	0.612
Target lesion	0%	10%	0.237
Nontarget lesion	3%	0%	1.000
CABG	0%	3%	1.000
Stent thrombosis	0%	0%	NA

NA indicates not applicable because of zero value.
*There were a total of 4 MACE events in 3 patients (0.13 event frequency). One patient had 2 events.

4 patients in the TAXUS group and 6 in the control group. The 30-day MACE rate was 0% in both groups.

The 6-month MACE rate was 0% (0 of 31 patients) in the TAXUS group compared with 7% in the control group (2 of 30 patients) (P=NS). These two MACE events in the control group were TLRs. One patient had LAD in-stent restenosis with unstable angina at 106 days treated by PTCA. This patient subsequently had CABG at 198 days for recurrent restenosis adjudicated as a second MACE event. The second patient had recurrent angina at 167 days associated with LAD in-stent restenosis treated with atherectomy. As shown in Table 3, the 12-month MACE rate in the control group was 10% (4 events in 3 patients) in comparison with 3% (1 event) in the TAXUS group (P=NS).

Baseline Lesion Characteristics

Acute angiographic results were comparable between the two groups, as shown in Table 4. The mean RVD after the procedure was 2.99±0.46 mm, with lesion lengths of 10.70±3.27 mm in the TAXUS group. This was similar to the control group RVD of 2.94±0.52 mm and lesion length 11.89±4.93 mm.

TABLE 4. QCA Results

QCA In-Stent Lesion Characteristics	TAXUS	NIR Control	P
Before intervention			
RVD, mm	2.99±0.46 (31)	2.94±0.52 (29)	0.699
MLD, mm	1.30±0.4 (31)	1.23±0.43 (29)	0.557
%DS	56.51±12.26 (31)	57.82±13.24 (29)	0.692
Lesion length, mm	10.70±3.27 (31)	11.89±4.93 (29)	0.272
After intervention			
MLD, mm	2.95±0.34 (31)	2.87±0.43 (27)	0.443
%DS	6.12±9.49 (31)	9.84±7.06 (28)	0.096
6-Month follow-up			
MLD, mm	2.60±0.49 (30)	2.19±0.65 (29)	0.007
RVD, mm	3.02±0.47 (30)	3.01±0.53 (29)	0.899
%DS	13.56±11.77 (30)	27.23±16.69 (29)	<0.001
>50% Restenosis	0% (0/30)	10% (3/29)	0.112
Late lumen loss, mm	0.36±0.48 (30)	0.71±0.47 (26)	0.008
Loss index	0.22±0.29 (30)	0.45±0.29 (26)	0.004

Six-Month Angiographic Results

The 6-month angiographic in-stent binary restenosis rate was 10% (3 of 29 patients) for the control stent and 0% (0 of 30 patients) for the TAXUS stent (P=NS). Mean %DS at 6 months was significantly lower in the TAXUS group than in the control group (13.56% versus 27.23%, P<0.001). The MLD was significantly larger in the TAXUS group than in the control group (2.60 mm versus 2.19 mm; P=0.007). Late lumen loss and loss index were significantly improved in the TAXUS group (all P<0.009, Table 4).

As shown in the Figure, there was a significant improvement in the %DS within the stented area with no differences at the proximal and distal edges (5 mm from the stent margins) between the TAXUS and control groups.

Six-Month IVUS Results

The baseline IVUS characteristics were similar in both groups (Table 5). After the procedure, no significant differences were noted between the groups for minimal lumen area or neointimal hyperplasia. At 6 months after the procedure, the mean minimal lumen area in the TAXUS group was significantly larger than in the control group (5.6 mm^2 versus 4.8 mm^2, P=0.027). Neointimal hyperplasia was significantly less in the TAXUS group than in the control group (14.8 mm^3 versus 21.6 mm^3, P=0.028).

Covariate Analysis

Covariate analysis showed patients with concentric stenosis had lower late loss values than did those with eccentric stenosis (P=0.02). Other covariates, including diabetes, smoking, vessel location, tortuosity, and calcification, were not predictive of angiographic or IVUS outcomes.

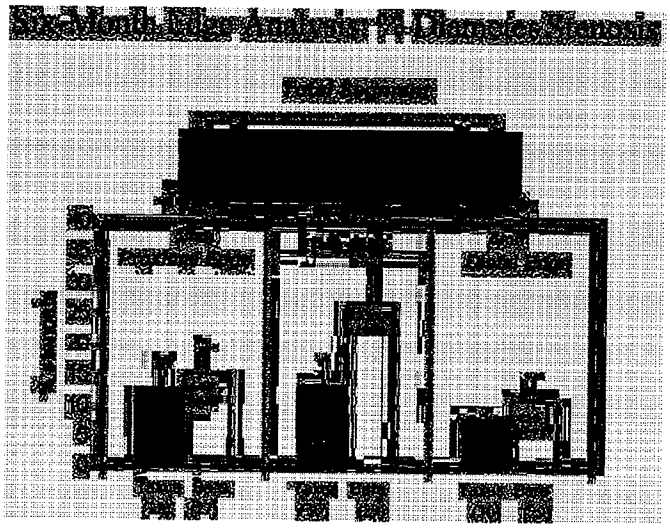
Discussion

This randomized, double-blind feasibility trial supports safety of the slow-release formulation of the TAXUS paclitaxel-eluting coronary stent in the treatment of coronary lesions at 1 year. There were no early or late stent thromboses in any study subject. MACE rates were low at 30 days, 6 months, and 12 months. The binary restenosis rate was 0% at 6 months; only 1 patient in this group had a target vessel revascularization, and that was for a lesion distal to the stented area.

Despite the small number of patients and excellent results in the control group, promising efficacy for the TAXUS slow-release formulation is supported by significant and concordant improvements in the QCA and IVUS parameters.

At 6 months, there were reductions in the %DS and late lumen loss compared with the control stent. This was confirmed by the IVUS data showing improvements in the minimal lumen area and normalized neointimal hyperplasia.

This drug-eluting stent system takes advantage of the antineoplastic agent paclitaxel incorporated into a unique slow-release, hydrocarbon-based elastomer polymer system to produce a controlled, biphasic release of this medication into the surrounding tissue. Paclitaxel is a microtubule-



Six-month %DS comparing in-stent and edge results. Error bars reflect 2× the standard error.

stabilizing agent with potent activity against proliferation, migration, and signal transduction.[3,5,6,7] The biphasic polymer-controlled drug release of this stent design, providing an early burst release in the first 48 hours followed by a slow release for the subsequent 10 days, appears to attenuate neointimal formation. Blood samples showed no systemic levels of paclitaxel with this slow-release formulation.

Several studies evaluating drug-eluting stents loaded with different antiproliferative agents, such as sirolimus, have recently been published or are still ongoing (RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent [RAVEL], SIRolImUS-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions [SIRIUS]).[8] Reported by Sousa et al,[9] the first in-human experience with a sirolimus-coated stent confirmed a profound reduction of neointimal volume with absence of stent restenosis for up to 1 year in the drug-coated stent group. The randomized, multicenter RAVEL trial compared a bare metal stent and the sirolimus-coated BX Velocity stent (140 $\mu g/cm^2$), demonstrating at 6 months' follow-up a restenosis rate of zero in the drug-coated stent group and a lumen loss of -0.01 ± 0.33 mm in the sirolimus group versus 0.80 ± 0.53 mm in the control group. There was no TLR, and the event-free survival rate at 1 year was 94.1% versus 70.9%.[10]

The persistence of extremely low MACE rates without stent thrombosis or TLR at 12 months in TAXUS I is encouraging. These promising data contrast with reports on the QuaDDs stent system, a high-capacity delivery system involving ≤5 polymeric sleeves per stent to provide ≤4000 μg of 7-hexanoyl taxol (QP2, a taxane derivative). Two problems have been reported: very late stent thrombosis (>6 months after implantation) and disappointing 12-month restenotic findings.

Liistro et al[11] reported a case of late total occlusion, 7 months after implantation of a QP2-eluting stent, presenting

TABLE 5. IVUS Results

IVUS In-Stent Lesion Characteristics	TAXUS	NIR Control	*P*
Before intervention			
MLA, mm^2	3.2±0.6	2.9±0.5	0.123
Vessel volume, mm^3	232.9±65.4	196.9±69.8	0.081
Lumen volume, mm^3	86.9±20.8	74.1±24.0	0.062
After intervention			
MLA, mm^2	6.97±1.69	6.36±1.55	0.165
Normalized vessel volume, mm^3	282.1±70.1	261.8±70.4	0.294
Normalized lumen volume, mm^3	119.1±27.7	113.0±25.2	0.408
6-Month follow-up			
MLA, mm^2	5.6±1.2	4.8±1.3	<0.027
Normalized vessel volume, mm^3	286.0±50.3	270.7±61.6	0.335
Normalized lumen volume, mm^3	107.7±19.2	98.0±26.4	0.135
Normalized neointimal hyperplasia, mm^3	14.8±10.8	21.6±10.7	0.028

MLA indicates minimal lumen area.

as an acute coronary syndrome after interruption of ticlopidine treatment. One potential mechanism for the very late thrombosis could be discontinuation of antiplatelet therapy when ongoing drug effect prevented adequate neointimal coverage over bare stents to pacify the surface. Liistro et al[12] have also reported results from a 15-patient, single-arm, in-stent restenosis registry in which acceptable 6-month outcomes were followed by disappointing 12-month restenotic data in ≈60% of patients. These reports suggest that the polymer sleeves, milligram doses of 7-hexanoyl taxol, and/or protracted drug delivery from the stent could delay healing or even aggravate the restenotic process.

The design objective of the TAXUS stent system is to use the minimum effective dose for the shortest duration by controlled biphasic drug delivery targeted for the initial phase of the restenotic process. In the TAXUS I study, the absence of TLR at 12 months suggests that the amount and rate of paclitaxel release disrupts the restenotic cascade while allowing sufficient neointimal growth to promote healing and avoid late thrombosis. Ongoing clinical follow-up in the present and the ongoing TAXUS trials on the NIR stent platform (TAXUS II, III) or the EXPRESS stent platform (TAXUS IV, VI) for more complex lesions should provide data on the clinical value of the technology.[8]

Limitations

Although the present study was a prospective, multicenter, double-blind, randomized trial, several limitations are noteworthy. The trial was conducted at only 3 sites where 31 patients with standard-risk lesions received the slow-release formulation of the TAXUS stent. The control group had excellent clinical and angiographic outcomes that may have limited the ability to identify significant differences with the TAXUS stent. IVUS guidance and extended use of clopidogrel may have contributed to the strong performance in both groups.

Other limitations include the prohibition of multiple stenting and the exclusion of high-risk patients. Given their high restenosis rates, high-risk patients are most likely to realize the greatest benefit from drug-eluting stents. Hand-crimping was employed in this study, potentially introducing the risk of drug displacement and contamination. Nonetheless, no MACE were clearly attributable to such potential risks.

Conclusion

In this feasibility trial, the slow-release formulation of the TAXUS stent offers the possibility of delivering paclitaxel to the target lesion and inhibiting postprocedural neointimal proliferation without adverse local or systemic effects. Larger studies of this promising technology are needed.

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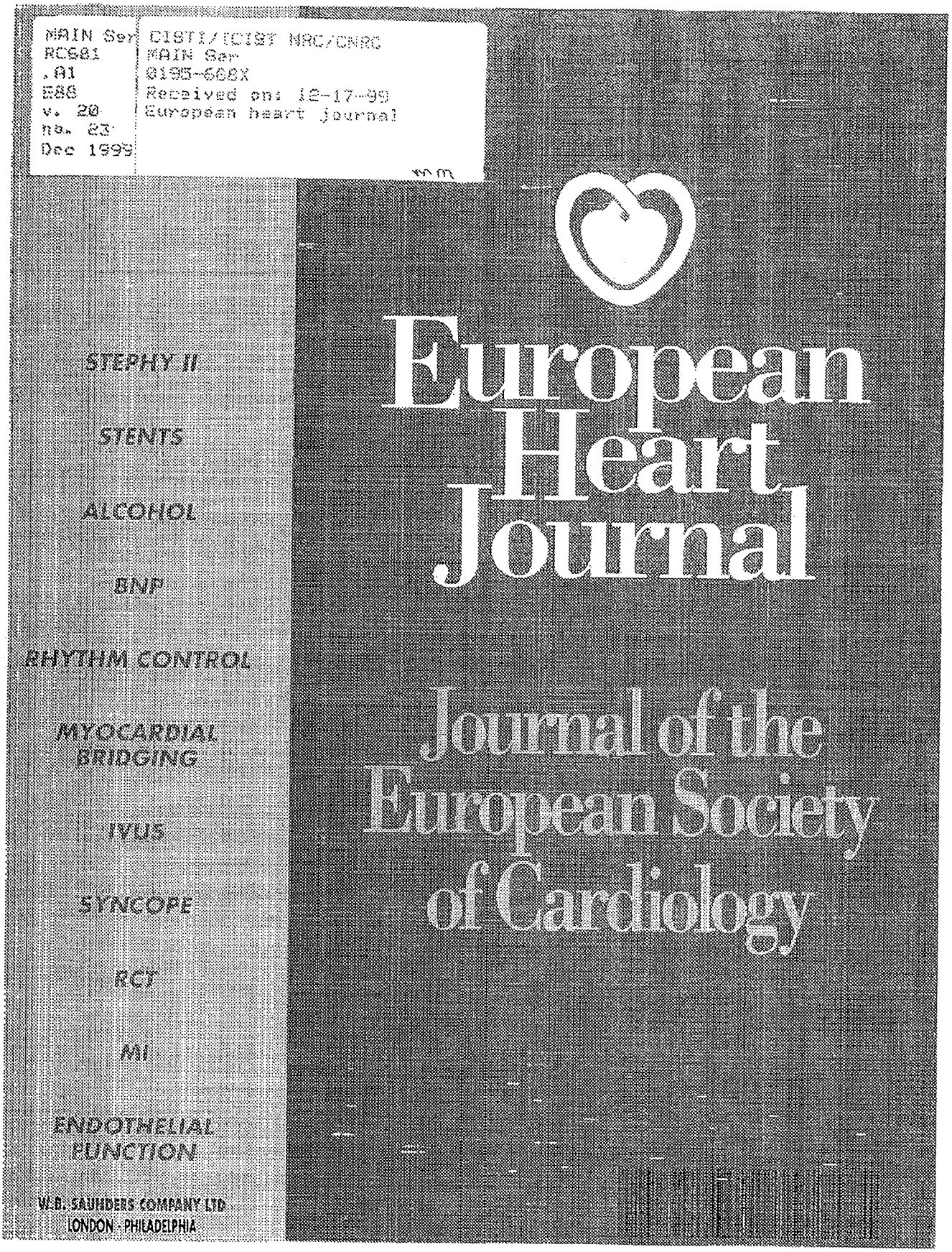

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Review Article

Stent coatings and local drug delivery

State of the art

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Why we need coatings and drugs

The new enemy of percutaneous intervention is in-stent restenosis. He joins the old enemy, restenosis after balloon angioplasty, who, after 21 years of resistance, refuses to capitulate. Unlike restenosis after balloon angioplasty, in-stent restenosis is a consequence almost entirely of tissue hyperplasia, occurring principally around the points where the stent struts impinge upon the artery wall[1]. Less common, but troublesome when it occurs, is subacute thrombosis, a complication not quite eliminated by modern stent deployment techniques and anti-platelet agents. These two factors are particularly limiting in diffuse disease, small vessels and arteries with poor run-off. Stenting, therefore, presents both the need and the opportunity for local drug delivery. Whilst the struts may create the problem, they may also present the solution, by carrying a coating or drug targeted at the thrombotic or hyperplastic responses occurring locally.

Methods of drug delivery

How may drugs be delivered in the context of stent implantation? There are three basic routes. First, drug may be absorbed into a suitable stent material itself, which is intended to act rather like a sponge. Release of the drug is dependent upon diffusion down a concentration gradient, or upon biodegradation of the stent material. Second, drug may be chemically bonded onto the surface of the stent struts and released after further chemical or biological action of the surrounding milieu or tissue. A coating on the stent may, of course, be regarded as a drug (in the loosest sense); albeit one which is intended to remain attached to the stent and confer desirable properties of haemocompatibility or biocompatibility ('presentation' of drug on a coating). A combination of this and the last approach may be attempted with a coating, for example a polymer with the necessary tertiary structure, which may be used as a depot for a drug to be held and released, the characteristics of uptake and release being controllable by the composition of the coating ('elution' of drug from a coating. Third, stent implantation and drug delivery can be treated as separate procedures. A dedicated local drug delivery catheter may be deployed to deliver drug intramurally, either before or after stent placement. This is termed adjuvant local drug delivery. The three methods may be combined. In this review, we will sub-divide stent-related local drug delivery into these three categories.

Drug delivery, not brachytherapy

It is appropriate to recall that therapeutic modalities other than drugs and coatings, for example local radiotherapy, may be applicable to stenting. Local radiotherapy is undergoing clinical trials at present, using the approach of either implanting a stent incorporating a suitable isotope with a short radioactive half-life into the stent struts, or treatment of the lesion site with a dose of radioactivity from a temporarily placed endoluminal wire. Both β and γ emitters are being studied, and at the time of writing it is unclear which is superior. It is also the case that, however remarkable the reduction in neointimal growth after such treatment in animal models, there remain doubts about both the long-term efficacy and safety of endoluminal radiotherapy. Discussion of this large topic is beyond the scope of this paper.

Development of drug delivery systems

Local drug delivery in association with stenting is currently active at three stages of development. First are the

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coatings and drugs which are sufficiently advanced to be the subject of clinical trials. These include surface-presentation of agents such as heparin, selected polymeric and inorganic coatings and adjunctive local delivery, via 'leaky' balloon, of anti-proliferative agents such as antisense oligonucleotide to the transcription factor *c-myc*. Second, more numerous and innovative but less proven in efficacy, are the coatings and drugs which are the subject of animal studies. There are, currently, dozens of these. Third, and highly novel and speculative, are the concepts which are still at the stage of laboratory bench testing, many of which will never achieve success in the clinical arena. Development of viable local drug delivery systems in the context of stenting requires the development of two (or even three) technologies together; stent design and manufacture, coating technology and drug pharmacology. Expertise in these areas has, heretofore, traditionally been concentrated in separate companies. Yet the regulatory bodies demand that a device with a drug constitute a combined therapeutic 'entity'. This is difficult for both the regulatory body and the companies. To stay at the cutting edge in a competitive market, either mergers or deals must take place between organizations with the relevant experience and the regulatory bodies must provide a streamlined path for overseeing safety in a fast-moving field.

Polymer stents

Questions of stent strength, effect on flow and efficiency and duration of delivery wholly from non-metallic substances have been addressed using in vitro flow models of various kinds. Stents entirely constructed from Type I collagen in a compliant, self-expanding form revealed insignificant resistance to flow in vitro[2], but in vivo studies warned of a severe tissue reaction with some polymers. A polyethylene terephthalate braided-mesh stent produced an inflammatory reaction, although the volume of tissue generated did not exceed that seen with metal stents[3]. Stents constructed completely from polyethylene terephthalate led to frequent thrombosis and marked late proliferation[4] with poor support[5].

Polymer-coated stents

Polylactic acid, polycaprolactone and ethylvinylacetate, when presented on a metal backbone, stimulate the growth of an unacceptably thick neointima in porcine coronary arteries[6]. Yet it appears that not all polymers are detrimental. Polyorganophosphazene coating led to an average 81% arterial stenosis compared with 32% for polyurethane and 39% for bare metal[7]. Polyurethane-coated nitinol stents exhibited no excess reaction over uncoated stents in rabbit carotid arteries[8], and polytetrafluoroethane was associated with a reduction in neointima[9]. More recently, biological mimicry has been introduced into the design of synthetic polymers, with interesting results. An example of this novel approach is phosphorylcholine. Phosphorylcholine is a Zwitterionic (neutral, but with balanced charges), hydrophilic phospholipid and a normal constituent of the cell membrane. Manufacture of clinically useful, stable phosphorylcholine is by mixture of it with methacrylate, triggering a thermal reaction in which the co-polymer methacrylo-phosphorylcholine-lauryl-methacrylate is produced. Phosphorylcholine polymer may then be physically adsorbed onto stent steel and exposed to γ radiation which both cross-links the polymer and sterilizes the stent. The average thickness of phosphorylcholine polymer on a stent is 50 nm and its weight 20 μg. Elastic and friction studies show that phosphorylcholine adheres well, even after balloon expansion of a stent. In vivo baboon and porcine studies have demonstrated its safety, thromboresistance and long-term biological neutrality[10–13]. The vascular response reaction to implanting uncoated and phosphorylcholine-coated stainless steel, balloon-expandable stents of up-to-date design in the porcine coronary artery at modest oversize showed minimal and equal neointima formation in both groups[14]. The cross-linking process allows the phosphorycholine to contain domains where drugs can bind; a fertile area for future research. It can also be applied in single or multiple layers. Phosphorycholine has been applied to the BiodivYsio stent (Biocompatibles). In the BiodivYsio registry, with open inclusion criteria, 270 unselected patients had a 30 day rate of major adverse cardiac events of 4·4%. The equivalent value for the heparin-coated Palmaz-Schatz stent (Cordis) in Benestent-II was 3·9%[15–16].

Membrane-covered stents

A complete polymer membrane has been applied as a sandwich between two Jostents (JoMed). This system is designed for repair of vessel rupture and coverage of thrombotic and degenerate plaques in old aorta-coronary vein grafts, aneurysms and arterio-venous malformations. Early reports of its use in such a group suggest that it is safe and feasible[17,18]. Its bulky profile and relative stiffness are constraints to widespread use, however, though the concept of complete plaque coverage is intriguing.

Drug-eluting stents (Fig. 1)

The aggressive inflammatory reaction seen with stents manufactured wholly from non-metallic (organic) substances has resulted, understandably, in few studies using this technique as a platform for local drug delivery. One of the very few studies was in the field of gene therapy. Polylactic acid/polycaprolactone tubes soaked in a solution of recombinant adenovirus and implanted into rabbit carotid arteries produced transgene

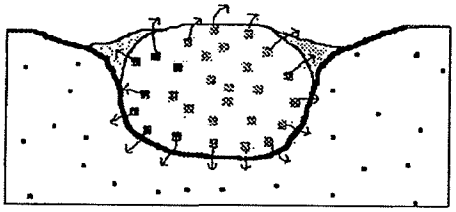

Figure 1 **Elution of drug from a biodegradable stent.**

expression in the media and adventitia at day 5[19]. Paclitaxel- and hirudin-coated biodegradable stents, when placed in a culture of smooth muscle cells obtained from human coronary atherosclerotic plaque, produced severe destruction of cytoskeletal components of the cells, suggesting a possible strategy for in vivo use, assuming the problems of inflammation and radial strength can be overcome[20].

Drug-presenting stent coatings

The most elegant, simplest and, probably, cheapest option for local drug delivery in the context of stent implantation is the use of a drug-presenting or eluting coating on a metal stent. Much experience has now been gained with heparin, with its anti-thrombin and, at least in vitro, anti-proliferative effects.

The Benestent-II pilot study and randomized trial used the Palmaz-Schatz (Cordis) stent with Carmeda (multiple layers of polyamine and dextran sulphate) surface-covalently-end-bonded heparin. In the final 50 patients in the pilot study (who received no systemic heparin after the implantation), 92% patients were event-free (compared with 80% in the Benestent-I stent group), with 0% bleeding (compared with 13% in Benestent-I)[21]. Final results from the trial (n=827 randomized) revealed a clinical event rate of 13% at 6 months compared with 19% in the PTCA group, and a reduction in restenosis (defined as >50% stenosis) from 31% to 16% in the stent group ($P<0{\cdot}001$)[16]. Other, far smaller trials, yield supportive data for the use of heparin coatings[22]. In one series of heparin-coated Wiktor (Medtronic) stents, the clinical event rate was 2/100 patients at 30 days[23].

The 1/621 sub-acute thrombosis rate in Benestent-II stimulated a trial of heparin-coated Palmaz-Schatz stents in acute myocardial infarction. In the pilot series, procedural success was 97% without lytic therapy or significant use of GPIIb/IIIa inhibitors, with major adverse cardiac events in 2/101 patients[24]. These are unquestionably excellent results. But it should be noted that Benestent-II-type trials primarily compare modern stenting methods (achievement of a large lumen with thorough stent deployment plus a Carmeda coating) with PTCA in a highly selected group of patients, rather than comparing coated and non-coated stents. Furthermore, the heparin in these studies may be regarded as a stent 'coating' rather than a local drug delivery system designed to elute.

Other heparin-containing coatings have been studied. A reduction in indices of thrombus formation (labelled fibrinogen and platelets and clot weight), but not neointima, was found with Palmaz–Schatz stents coated with Duraflo II (heparin on a hydrophobic binding agent)[25]. Acute benefit without reduction in late neointima has been a consistent finding with heparin coating of various kinds[26–30]. An exception to this rule has been bonded heparin on the Cordis stent in the baboon carotid artery, where neointima was reduced at 30 days[31].

Drug-eluting coatings (Fig. 2)

More potent anti-thrombotic agents alone, and combined with anti-platelet agents, have been examined. A polylactic acid coating containing hirudin and prostacyclin demonstrated freedom from thrombus in a human stasis model[32]. The potential for elution of drug, when maintenance of local levels was the aim, has been a concern. Hirudin and iloprost (a stable prostacyclin analogue) on a polylactic acid-polyethylene glycol coating, in flowing human plasma, retained an anti-thrombotic effect for more than 30 days[33]. When Palmaz–Schatz stents with this coating were implanted in sheep coronary arteries, neointima was reduced by 30% compared with uncoated stents ($P<0{\cdot}05$)[34].

The use in stent coatings of local GPIIb/IIIa inhibitors, a class of drug already shown to be valuable when given systematically, tests the hypothesis that blocking the receptors on platelets adherent at the site of injury may be sufficient for a local effect, whilst avoiding bleeding complications. Cross-reaction with the $\alpha v\beta 3$ integrin receptor may also have a beneficial effect on cell proliferation and restenosis. Retention of such an agent is possible; 48% of a dose of the 7e3 antibody to IIb/IIIa was held in a polymer coating on stent wires in a flow model for 8 days[35]. It may be retained on the stent despite sterilization and storage[36] and is capable of reducing platelet deposition on the stent[37]. In a parallel model, urokinase and the IIb/IIIa antagonist AZ1 retained 19 and 38% activities at 10 days, respectively[38]. A composite stent containing IIb/IIIa inhibitor reduced platelet adhesion in dog coronary arteries by 65% at 2 h ($P=0{\cdot}01$)[39]. A similar study, with the antibody absorbed into a polymer coating on stents implanted in rabbit iliac arteries, demonstrated 0/10 vessels occluded at 28 days in the antibody group compared with 3/5 animals in the base polymer group and 3/5 in a group treated with an unrelated antibody. There was a non-significant trend towards reduction of in-stent restenosis in the antibody-treated group[40]. When conjugated with urokinase, an enhanced local anti-platelet effect was observed, with less cyclic flow variation than in control stents[41].

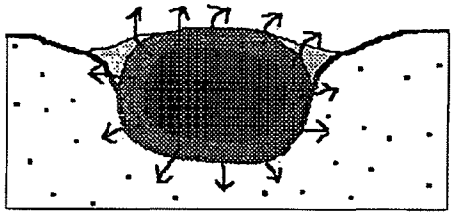

Figure 2 **Presentation of drug on, or elution of drug from, a stent coating.**

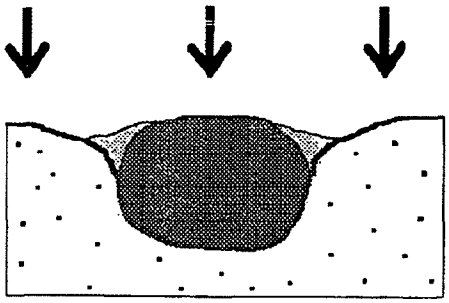

Figure 3 **Adjuvant delivery from a separate, dedicated, drug delivery catheter.**

Angiopeptin, a synthetic octapeptide and analogue of somatostatin, has been shown to reduce the tissue response to growth hormone, insulin-like growth factor and interleukin-1-mediated endothelial cell adhesion. Encouraging results from systemic delivery have been reported in terms of reduced clinical events after PTCA in clinical trials[42,43] and in terms of neointimal growth in a porcine coronary artery stent model[44]. Wiktor stents which had been coated with the biodegradable polymer poly-organophosphazene, were loaded with angiopeptin and implanted in porcine coronary arteries. Angiopeptin was retained for a clinically useful period, and the minimum lumen diameter was increased by 40% and morphometric lumen area by 132% ($P<0.01$)[45]. Our group has shown that angiopeptin may be absorbed into the phosphorylcholine coating of a BiodivYsio (Biocompatibles) stent, with 43% of the administered dose retained in the stent or the adjacent tissue at one week[46]. Angiopeptin has also been given by adjuvant local delivery (see below).

It is apparent from both necropsy specimens and animal studies that the early period after arterial balloon injury is dominated by both thrombotic and inflammatory processes. Steroids, given locally, might, therefore, be expected to have a beneficial effect upon the vascular reaction to stenting. Steroids in stent-based local drug delivery have, however, shown somewhat mixed results in animal studies. A polylactic acid matrix loaded with dexamethasone has been applied to Wiktor stents implanted in pig coronary arteries. The local concentration was 3×10^5 higher than in the serum at 24 h, and 3×10^3 higher at 28 days. Despite this, there was no significant reduction in neointima at 28 days[47]. Methylprednisolone in an organophosphazene matrix on a metal stent in porcine coronary arteries did show a 22% reduction in area stenosis ($P=0.002$), but this may have been because this polymer, without the steroid, induces a severe histiolymphocytic and fibrocellular reaction[48].

Other agents have been studied in animals. The tyrosine kinase inhibitor ST638 has been absorbed into a PLA stent and implanted into porcine coronary arteries. Minimum lumen diameter was increased by 46% compared with control ($P<0.01$)[49]. The microtubule-stabilizing agent paclitaxel (Taxol), already used in cancer chemotherapy, was applied to a chondroitin sulphate and gelatin biodegradable polymer and coated on the Gianturco-Roubin II stent (Cook). When implanted in pig coronary arteries, it produced a 40% reduction in neointimal thickness ($P<0.05$); whereas, in the same study, dexamethasone, dexamethasone with heparin and angiopeptin failed to produce such an effect[50]. A similar study in rabbit iliac arteries also showed a significant reduction in neointima[51]. A polynitrosated albumen NO donor, dip-coated onto Palmaz–Schatz stents, reduced platelet adhesion by a factor of 4·5, and increased the lumen area by 37% in pig carotid arteries at 7 days[52]. Activated protein C, a potent endogenous anti-thrombotic agent, was applied to stent wires in vitro, and resulted in a significant reduction in fibrin deposition[53].

Adjuvant local drug delivery (Fig. 3)

In the field of adjuvant local drug delivery, early experimental work preceded the technological development of endoluminal delivery catheters. Seminal work showed that heparin released from perisvascular ethylene-vinyl acetate copolymer placed around denuded rabbit iliac arteries, into which stainless steel stents had been implanted, was associated with a sub-acute thrombosis rate of 0/9 vessels compared with 3/10 controls ($P<0.05$). There was also a 46% reduction in neointima area compared with controls[54]. Since then, experience has been accumulating with 'weeping' balloon devices. These are capable of delivering volumes of drug many orders of magnitude greater than that contained within a stent coating. The HIPS trial used an infusion of 5000U heparin via either guide catheter or InfusaSleeve (LocalMed) prior to implantation of a Palmaz–Schatz stent, with clinical, angiographic and intravascular ultrasound end-points. No reduction in in-stent neointimal volume was seen; but useful safety data was obtained[55]. Bartorelli and colleagues also found no reduction in late lumen loss in 35 patients who received 2–4000U heparin via the InfusaSleeve catheter after pre-dilatation but before stent placement[56].

Low molecular weight heparin has also been studied. When delivered locally via an iontophoretic catheter prior to oversize stenting in porcine coronary arteries, low molecular weight heparin produced no injury or

change in neointimal thickness additional to that seen after stent implantation alone[57]. The POLONIA study randomized 100 patients to 10 000 units heparin i.v. or 2500 units heparin i.v. plus 10 mg enoxaparin delivered to the lesion through a Transport (Boston Scientific) catheter during lesion pre-dilatation. Early reports suggest a significant reduction in neointima formation in the locally-treated group at 6 months in the first 64 patients studied[58].

Methylprednisolone (60 ± 23 mg) was delivered via the Infiltrator (intra-mural micro-injector catheter, InterVentional Technologies) prior to stenting in 36 lesions. Major procedural events dominated the results of this trial. The catheter failed to cross the lesion in 10% and there was non-Q wave myocardial infarction in 8%, sub-acute thrombosis in 3% and restenosis in 40%[59]. These relatively poor results, however, may relate more to imperfections of the drug delivery system employed than the drug delivered.

The ITALICS study built on the efficacy of antisense oligonucleotide to the proto-oncogene *c-myc* in animal models of restenosis after PTCA. The agent was given via the Transport (Boston Scientific) catheter after successful Wallstent (Schneider) placement in 80 patients. The primary end-point was neointima volume assessed by intravascular ultrasound at 6 months. This was potentially a landmark trial; the first in which genetic material was applied to modify a disease state in the coronary arteries. Local delivery would seem to be particularly suited to the requirements of a trial such as this. Nevertheless, the results were negative, with no significant difference between the control and antisense groups in any parameter[60]. This has stimulated lively debate as to whether the drug lacks efficacy, whether the mode of delivery (with all the attendant variables such as dose, volume, timing –before or after stent placement—efficiency, retention, washout, degradation etc.) was imperfect or whether the study design, with a control group without fluid delivery, masked a positive biological effect of the antisense. Perhaps the cardinal problem in the design of this study was the use of the Wallstent, which is capable of maintaining chronic stretch in the artery weeks after deployment (and, therefore, weeks after local drug delivery).

Other promising agents studied in the context of adjuvant drug delivery include angiopeptin. In an outstanding study, when delivered via the Dispatch catheter, systematically or by both routes, to the site of implantation of Palmaz–Schatz stents in pig coronary arteries, a significant reduction in neointima formation compared with control was observed in all three treatment arms[61]. Another chemotherapeutic agent studied in a similar porcine coronary artery model is paclitaxel. When delivered via the Infusasleeve in the context of stent placement, no significant reduction in in-stent neoitima was found[62]. An elegant approach is to passivate the stented endoluminal surface by accelerating endothelialization. Naked plasmid DNA encoding for vascular endothelial growth factor was delivered via a hydrogel polymer-coated balloon after implanting Palmaz–Schatz stents in intimally denuded rabbit iliac arteries. At 7 days there was 87% endothelial coverage in the treated stents compared with 33% in the controls (P=0·005), and a 54% reduction in intimal area at 28 days (P<0·0001)[63]. Entire cells may also be 'sodded' onto stented vessels. Endothelial cells have been infused via the Dispatch catheter into the site of Palmaz–Schatz stent implantation in rabbit iliac and pig coronary arteries, with 82% endothelial coverage at 4 h (compared with 0% in controls); although both groups showed >90% coverage at day 14[64]. The very success of this type of experiment raise the question as to the validity of stent polymer coatings; by enhancing biocompatibility, do they delay endothelialization and, in the end, do more harm than good? Preliminary data from the phorphorylcholine-coated BiodivYsio stent (Biocompatibles) in the porcine coronary artery suggests that there is no delay in re-endothelialization[65].

As for the best timing of adjuvant delivery, there are a number of issues to consider. Delivery could be before or during pre-dilatation (as performed, for example, in the POLONIA and HIPS trials). The delivery catheter in these cases is probably tight against the lesion, but possibly lacking in apposition elsewhere, with the potential for excess drug loss downstream. Delivery after pre-dilatation may take advantage of increased uptake in areas of mural damage. The balloon/artery ratio would, however, be speculative, with more potential for downstream losses. Delivery after stent deployment (as used, for example, in the ITALICS trial) would minimize the variance in the device-artery ratio, but the risk would be of spoiling an otherwise good stent implantation, because there are indications that fluid delivery *per se* can exacerbate neointima formation[66].

Autologous vein and other 'natural' coatings

A completely different approach has been to apply an autologous vein graft to stents. When implanted in porcine iliac arteries, vein-covered Palmaz–Schatz stents exhibited no thrombus and complete endotheial coverage. Mild atrophy of the media was also noted[67]. Whilst requiring time and skill to prepare, this technique has been used in 35 patients with complete procedural success and no cases of sub-acute thrombosis[68]. In the porcine coronary artery, neointima was reduced with this approach[69]. The Athens group, with the greatest experience of this technique, reported that 89% of a selected population treated with this technique were event free at two years[70]. In a retrospective, comparative study, they described a reduction in late loss of lumen diameter in a vein-covered stent group (n=55) compared with a conventionally stented group[71]. There is a report, however, of increased late loss with this technique[72]. The potential advantages of this approach may lie in reducing vascular injury[73] or of isolating the damaged vessel wall from the blood. Fibrin coating may

also reduce thrombus formation. A fibrin-covered sleeve has been applied to metal stents and implanted in porcine coronary arteries. Three out of 31 of these were occluded by 28 days compared with 12/12 polyurethane controls[74]. A fibrin covering on tantalum stents in pig coronary arteries, shown to degrade over months, showed no excess vascular reaction[75]. When fibrin was loaded with RGD peptide (an inhibitor of platelet-fibrinogen interaction) on a novel stent in the atherosclerotic rabbit, neointima was reduced by 79%[76].

Inorganic coatings

Inorganic strategies may also have potential. Silicon carbide has been investigated for its ability to alter the electro-chemical properties of the stent surface. It has been suggested that the initiation of thrombosis is at least partly due to degeneration of blood proteins by electron transfer to the metal. The ideal surface, from this point of view, is a semi-conductor such as silicon carbide. But, being brittle, silicon carbide can only be applied as a thin layer. Systematic testing of the effect of the silicon-carbide coated Tensum (Biotronik) stent upon cytotoxicity, haemolysis, mutagenicity and haemocompatibility produced favourable results when compared with Palmaz–Schatz (Cordis) and HepaMed (heparin) coated Wiktor (Medtronic) stents[77]. Tantalum stents, coated in the compound, were deployed in rabbit iliac arteries. Complete endothelialization with minimal intimal proliferation was observed[78]. Placement of eight silicon carbide-coated Palmaz–Schatz stents into patients suffering from abrupt closure post-PTCA showed, at coronary angiography the next day, patency of all the stents with no visible thrombus[79]. A series of 165 patients with 215 stents has now been published using the Tensum (Biotronik) tantalum, balloon expandable, silicon carbide-coated stent deployed in a group at high risk of restenosis and thrombosis. There were 2% stent thrombosis. At six months, 32% of patients (24% of stents) had had a cardiac event[80]. Notwithstanding this disappointing result, other inorganic coatings demonstrate useful properties. A 'diamond-like' carbon-coated stent (not, therefore, strictly speaking, inorganic), exposed to flowing, platelet-rich plasma produced less platelet activation and deposition and ion release than uncoated stents[81,82]. Gold would seem to be the ultimate inert stent coating. A 5 μm thick gold coating was applied to a stainless steel stent and, indeed, showed more than a halving of adherent thrombus mass compared with an uncoated stent[83]. But, disappointingly, a randomized study of 730 patients receiving a gold-coated or bare stent revealed an excess of clinical events in the gold-coated group at one year (24% vs 13%)[84].

Conclusions

There may well be a role for local drug delivery in the era of stent implantation. Retention of a metal core to maintain the ability to scaffold the artery seems likely for the foreseeable future. Polymers simply do not have the right physical strengths, and many of them elicit an inflammatory reaction. A coating alone appears insufficient to prevent in-stent restenosis, but may be used as a vehicle to deliver an anti-proliferative drug, rather than simply being biologically 'neutral'. Excellent haemocompatibility alone, though, might prove useful in adverse conditions predisposing to subacute thrombosis. As a carrier, the coating may be required to carry (stably, in storage), hold (for a biologically relevant period of time *in vivo*) and elute (slowly, into the wall of the artery) sufficient drug to have a useful local effect, without loss by friction with the catheter or artery or washout into the bloodstream. A tall order, by any standards, especially when it is realized that metal coverage is typically only 10–20% of the surface area of the vessel. It may, indeed, be an impossible order for a thin coating. The answer may lie with adjuvant local drug delivery. The argument then becomes practical and economic. Is a reduction in in-stent restenosis worth the trouble, time and extra expenditure on adjuvant drug delivery via a separate catheter? Technology may help here. A 'dream ticket' might be a single device for pre-dilatation, stent implantation, post-dilatation and intra-mural delivery together with a drug-eluting stent coating for longer-term, even more highly localized delivery. Some of the currently available devices, coatings and stents are getting close to making this aim an achievable reality.

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Acute and one year follow-up results after vessel size adapted PTCA using intracoronary ultrasound

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Aims Recent randomized clinical trials have reported a reduction in restenosis with intracoronary stents and have suggested that this restenosis reduction is a result of the higher immediate luminal gain, in comparison to conventional percutaneous transluminal coronary angioplasty (PTCA). The hypothesis of this study is based on the assumption that PTCA results may be optimized by determining vessel dimensions before intervention, using intravascular ultrasound. This may lead to long-term PTCA results equivalent to PTCA and the additional placement of a stent. The purpose of this prospective non-randomized single-centre study was to evaluate (1) the safety and efficacy and (2) the long-term outcome of vessel-size adapted PTCA in patients with native coronary artery obstructions.

Methods and results From January 1995 to December 1995 the morphological dimensions of target lesions were determined in 144 patients with 152 lesions by intravascular ultrasound prior to conventional balloon angioplasty. Quantitative assessment of the vascular dimensions were assessed on-line and the diameter of the balloon catheter was adapted to the external elastic membrane diameter at the lesion site. Using this strategy, mean balloon diameter was 4·0 ± 0·5 mm and mean pressure for complete balloon expansion was 7 ± 2 atmospheres. Acute and one year follow-up results were obtained in all 144 patients. Acute events occurred in two patients (one death and one acute surgical revascularization). During one year follow-up, 16 patients (12%) had a clinical event including one cardiac death, two transmural myocardial infarctions, 10 repeat PTCAs within the target lesion and three elective coronary artery bypass grafts (CABG). In 75% (n:112) control angiography was performed and revealed an angiographic restenosis rate of 21% using the NHLBI criteria of a diameter stenosis >50%.

Conclusion Intravascular ultrasound provides an accurate and precise description of vascular dimensions at the site of the stenotic lesion. The use of balloon diameters following these measurements appears to be (1) safe in the acute setting with a low number of in hospital events and (2) gives a low restenosis rate and number of clinical events at one year follow-up. These promising results warrant verification in larger-scale randomized trials.
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Key Words: Balloon angioplasty, intravascular ultrasound, restenosis.

Introduction

Percutaneous transluminal coronary angioplasty is a widely used revascularization technique in patients with coronary artery disease, but is limited by a restenosis rate ranging from 30% to 50%[1–7]. Stents have been developed to improve the acute, and long-term results of coronary angioplasty. Compared to conventional balloon angioplasty, stents have demonstrated their ability to reduce restenosis in several randomized clinical trials with restenosis rates between 22% to 32% during 6 months follow-up[8,9]. The reduction in restenosis rates following stent implantation was mainly attributed to the improved luminal diameter, in comparison to conventional balloon angioplasty using quantitative angiographic analysis. However, numerous reports have shown that the assessment of vascular dimensions using intravascular ultrasound provides a more accurate measure than angiography especially in diseased vascular segments[10–16].

The safety of intravascular ultrasound with a very low rate of complications has been demonstrated previously[17,18]. It has been shown conclusively that this technique not only provides information on the extent, location, and composition of the atherosclerotic plaque but also permits exact visualization of arterial dimensions[19]. Lumen size, vessel wall morphology, and

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Table 1 Baseline clinical characteristics of the 144 patients included in the trial

Characteristic	n=144 (%)
Age (years)*	61 ± 9
Male sex	127 (88)
Female sex	17 (12)
Ever smoked	91 (63)
Current smokers	15 (10)
Diabetes mellitus	36 (27)
Myocardial infarction	78 (55)
Hyperlipidaemia	75 (52)
Hypertension	68 (47)
Exertional angina pectoris pre PTCA (CCS class)**	
I	44 (34)
II	67 (44)
III	28 (19)
IV	5 (3)

*Plus-minus values are means ± SD; **According to the classification system of the Canadian Cardiovascular Society (CCS).

dimensions as determined by intravascular ultrasound have been shown to correlate well with histopathological post-mortem examinations[20,21]. Since the reduction in restenosis rates using stents is thought to be the result of an improved acute minimal lumen diameter, in combination with a reduction of elastic recoil, optimized, intravascular ultrasound guided PTCA might also result in a reduction of restenosis during late follow-up. However, sizing of the balloon diameters using the external elastic membrane diameter at the lesion site might result in a high rate of vascular complications due to severe dissections and may not lead to a reduction of restenosis rates, although an 'optimal' balloon angioplasty was attempted. Thus, the aim of this prospective non-randomized single-centre study was to evaluate (1) the safety and efficacy and (2) the long-term outcome of vessel size adapted PTCA of patients with native coronary artery obstructions.

Methods

Patients

This prospective, non-randomized single-centre trial was initiated on 3 January 1995 and completed at the end of December 1995. One hundred and forty-four patients with 152 lesions, accounting for 23% of all angioplasty patients in 1995, were included in the study. In all patients morphological dimensions of the target lesion were determined by intravascular ultrasound prior to conventional balloon angioplasty. The patients' clinical and angiographic baseline characteristics are provided in Tables 1 and 2. The specific angiographic criteria for enrolment included an at least 70% stenosis, according to the estimate of the investigator and the absence of severe vessel angulations (>90°) pre- or at the lesion site. Reasons for study exclusion were left main stem disease, bypass graft lesions, restenotic lesions, total occlusions, type C lesions, vessel diameters of less than 2·0 mm as determined by angiography, and acute myocardial infarction. Vessel calcifications were not an exclusion criterion. Twenty-seven patients were excluded from the study, in whom the pre-interventional intracoronary ultrasound examination could not be completed with sufficient quality. The residual 144 patients had a clinical follow-up evaluation at least 12 months post-intervention with an angiographic follow-up rate of 75%.

All patients had given oral and written informed consent prior to the intervention. The protocol was approved by the Ethical committee of the University of Tuebingen.

Procedure

Prior to the intervention, baseline angiograms of the target lesion were recorded in at least two projections. The angiograms were stored on a computer disk of the biplane digital acquisition X-ray system (DCI, Philips, Inc., Eindhoven, The Netherlands). After the guidewire was introduced in the periphery of the target vessel and before angioplasty the vessel and lesion site were visualized with an ultrasound imaging catheter (Cardiovascular Imaging Systems Inc., Sunnyvale, CA, U.S.A.). The 30 MHz, 3·2 F diameter monorail ultrasonic catheter consists of a single ultrasound transducer at the end of a flexible motor-driven shaft with a mirror at 45° that reflects the beam perpendicular to the long axis of the catheter. Continuous ultrasound images were obtained as the catheter was moved back from at least 1 cm distal to the lesion site to the proximal part of the target vessel by slow manual pull-back. The position of the ultrasound catheter was controlled by fluoroscopy and displayed on the same videoscreen as the ultrasound images, to ensure correlation between cross-sectional ultrasound images and the position of the angiogram along the length of the artery. In addition, landmarks of the artery, such as calcifications, take off of side branches or specific stenosis patterns were used for identification of ultrasound catheter location. The images were recorded on super VHS videotape and stored on a computer disk. After the ultrasound images were obtained, the ultrasound catheter was withdrawn from the artery and balloon angioplasty was performed. Balloon sizing was performed by online measurements of the external elastic membrane in two perpendicular angles at the tightest lesion site as well as in the pre- and post-stenotic vessel segment. A balloon to artery ratio of 0·8 to 1 was considered to be optimal.

Before angioplasty (as the first step of the procedure), after angioplasty (as the last step of the procedure), and at follow-up (before any subsequent intervention), 0·2 mg intracoronary nitroglycerin was administered, and pre- and post-intervention a complete ultrasound imaging run was performed from beyond the target lesion to the aorto-ostial junction.

Quantitative angiographic analysis

All cineangiograms were analysed by two independent observers using the off-line analysis software QANSAD (ARRI, Munich, Germany). This method has been validated and described in detail elsewhere[22]. The outer diameter of the contrast-filled catheter was used for calibration. Minimal lumen diameter, minimal lumen cross-sectional area, percent diameter stenosis, reference diameter and reference cross-sectional area before and after the intervention were measured using multiple projections, and the results from the 'worst' view recorded[23]. The final balloon diameter was measured by using the flow chart provided by the balloon-company.

The mean variability for repeated measurements performed on different days was 0·12 mm for minimal lumen diameter and 3·8% for percent diameter stenosis.

Quantitative and qualitative intravascular ultrasound measurements

Validation of cross-sectional measurements by intravascular ultrasound has been reported previously[24–29]. By use of computerized planimetry, the external elastic membrane diameter, minimal lumen diameter and the minimal luminal cross-sectional area were measured at the lesion site[30]. The external elastic membrane cross-sectional area (which represents the area within the border between the hypoechoic media and the echoreflective adventitia) has been shown to be a reproducible measure of total arterial cross-sectional area[31]. When the atherosclerotic plaque encompassed the catheter, the lumen was assumed to be the physical size of the imaging catheter.

The occurrence of calcium was identified as plaque that was brighter than the reference adventitia with acoustic shadowing of deeper arterial structures. The arc of calcium was then measured with a protractor centred on the lumen. The extent of calcium deposition was considered as mild if the calcium arc occupied less than 180° of the vessel circumference. A lesion was considered as severely calcified if a calcium arc of more than 180° of the vessel circumference was present.

The same anatomical image slice was analysed before intervention, after intervention, and the differences were compared. By using one or more reproducible axial landmarks, identical cross-sectional slices could be identified for comparison. The anatomical slice selected for the serial analysis had an axial location within the target lesion at the smallest follow-up lumen cross-sectional area.

To account for reproducibility, all cross-sectional measurements were made by the same individual, who was blinded to the angiographic results. To assess reproducibility and intra-observer variability of sequential intravascular ultrasound measurements, a consecutive series of 30 pre- and post-intervention ultrasound studies were analysed at least 3 months later. This analysis included the error in repeatedly selecting the same image slice as well as the error involved in performing the cross-sectional measurements.

The differences in the pre-intervention measurements were as follows: external elastic membrane cross-sectional area (0·02 ± 0·08 mm^2) and lumen cross-sectional area (0·04 ± 1·01 mm^2). The intra-class correlation coefficient[32] for repeated pre-intervention measurements of the external elastic membrane cross-sectional area was 0·98 and of lumen cross-sectional area was 0·94. The differences in the post-intervention measurements were as follows: external elastic membrane cross-sectional area (0·03 ± 0·70 mm^2) and lumen cross-sectional area (0·13 ± 0·28 mm^2). The intra-class correlation coefficient for repeated follow-up measurement of the external elastic membrane cross-sectional area was 0·99 and of the lumen cross-sectional area was 0·96.

Definitions

Success

Angiographic success was defined as an increase of >50% in luminal diameter with a final percent diameter stenosis of <30% and no major complications. The following criteria determined by post interventional intravascular ultrasound were used to define a successful PTCA: (1) luminal cross-sectional area gain of at least 20% as compared to the external elastic membrane cross-sectional area and/or (2) ultrasonic evidence of a dissection creating a second lumen with an angiographically patent flow (TIMI 3) to the distal vessel segment that persisted 20 min after PTCA[27,33,34]. In this clinical situation with sufficient flow to the periphery of the target vessel, implantation of vascular stents was avoided. These criteria for intravascular ultrasound success were used in guiding the angioplasty procedure. Post-intervention angiographic evidence of dissections was defined according to the modified classification of the Heart, Lung, and Blood Institute[35].

Complications

The occurrence of repeat PTCA, bypass surgery, Q wave myocardial infarction, and death within the study period were considered major complications. The following criteria were considered as minor complications: transient in-lab vessel closure, side branch compromise, hypotension, transient atrioventricular blocks requiring the implantation of a pacemaker and reversible vasospasm of the target vessel.

Angiographic restenosis

The angiographic definition of restenosis was defined according to the NHLBI criterion as a follow-up diameter stenosis of >50%[36].

Statistics

The data were collected by the Clinical Study Centre (Medical Clinic III). After the closing of the database

the data were transferred to the Institute for Medical Information Processing, which performed the final statistical analysis.

Continuous variables were described by their means and standard deviations; discrete variables as counts and percentages. Missing data were excluded; the number of valid cases are given in the tables.

The incidence of major complications was determined in two ways: (1) considering all major complications and (2) considering only major complications, which had occurred as a result of restenosis or vessel occlusion at the site of the target lesion. Kaplan–Meier curves were plotted to describe the relationship between the clinical events and the time of their occurrence. Patients without end-points were censored at the time of the clinical follow-up.

To describe the change in minimal lumen diameter and in diameter stenosis from pre-PTCA to post-PTCA, and to follow-up angiography cumulative distribution curves were only plotted for patients in whom follow-up angiography had been obtained. To assess the value of intravascular ultrasound and angiography for the prediction of restenosis, the patient population was separated into two groups (with and without restenosis) and the distribution of these variables was compared using the Wilcoxon rank-sum test. Mantel–Haenszel chi-squared tests were conducted to define the optimal cut-off for characterizing risk groups. The point with the maximum chi-square was chosen as the cut off. All analyses were carried out using the SAS system for Windows.

Results

Acute clinical events

In-hospital events occurred in two patients. One patient suffered acute vessel closure of the left anterior descending artery despite therapy with GP IIb/IIIa antagonists; the attempt to place a stent at the lesion site was unsuccessful and the patient was transferred to immediate bypass surgery. Three days post surgery this patient died due to recurrent ventricular tachycardia and emerging left ventricular failure with the signs of extensive anterior myocardial infarction. The second patient suffered early reocclusion 3 h after PTCA and underwent primary successful re-PTCA within 1 h. Because of recurrent chest pain and triple vessel disease, he underwent successful bypass surgery 2 days later without any further event.

Following PTCA, contrast angiography detected dissections in 57% and intravascular ultrasound imaging revealed dissections in 67% of the patient population. The majority of these dissections (63%) were angiographically classified as type B or C. Only 11% were classified as type D or E. On intravascular ultrasound imaging, however, 68% of the dissections were classified as severe, thus fulfilling one of the two arbitrary criteria for acute success. None of these patients developed acute vessel closure and no vessel required the additional placement of a stent due to a severe dissection with impairment of flow (TIMI <3).

Serial angiographic results

Overall, the pre-intervention minimal lumen diameter measured $0{\cdot}50 \pm 0{\cdot}41$ mm and the diameter stenosis was $82{\cdot}2 \pm 12{\cdot}5\%$. The post-intervention minimal lumen diameter increased to $2{\cdot}23 \pm 0{\cdot}58$ mm, and the diameter stenosis decreased to $28{\cdot}6 + 12{\cdot}9\%$. Angiographic follow-up data were obtained for 75% of the eligible patients at a time interval of 12 ± 1 months (range 3 to 21 months). At follow-up, there was attrition in minimal lumen diameter to $1{\cdot}76 \pm 0{\cdot}81$ mm (see Fig. 1), with an associated increase in diameter stenosis to $36{\cdot}5 \pm 25{\cdot}1\%$ (see Fig. 2). Thirty one target lesions (21%) were classified as restenotic lesions (see Table 3).

Univariate analysis of angiographic predictors of restenosis at the $P<0{\cdot}05$ level (minimal lumen diameter, % diameter stenosis, and reference diameter pre- and post-PTCA) showed no statistical significance for late lumen narrowing. Other predictors, which were also not significantly associated with the incidence of restenosis, included (1) vessel tortuosity (2) pre-interventional TIMI flow 3 vs 2 (3) left anterior descending artery disease (4) ostial lesion location and (5) target lesion calcification.

Serial intravascular ultrasound measurements

Pre-intervention, the in-lesion site cross-sectional area was $1{\cdot}87 \pm 1{\cdot}3\ mm^2$ which increased to $5{\cdot}07 \pm 2{\cdot}45\ mm^2$ following PTCA. The minimal lumen diameter was $1{\cdot}46 \pm 0{\cdot}5$ mm pre-PTCA, which increased to $2{\cdot}38\ mm \pm 0{\cdot}81$ mm following balloon angioplasty, corresponding to a gain in luminal diameter of $0{\cdot}92 \pm 0{\cdot}93$ mm. External elastic membrane cross-sectional area was found to be $14{\cdot}5 \pm 6{\cdot}48\ mm^2$ pre-intervention and this increased to an external elastic membrane cross-sectional area of $17{\cdot}2 \pm 7{\cdot}4\ mm^2$ post-PTCA, indicating an over-extension of the stenotic vessel segment (see Table 4). The external elastic membrane diameter pre-PTCA was $4{\cdot}38 \pm 1{\cdot}63$ mm. The average balloon diameter was $4{\cdot}0 \pm 0{\cdot}5$ mm, corresponding to a balloon-to-vessel diameter (external elastic membrane) ratio of $0{\cdot}84 \pm 0{\cdot}11$ (see Table 5).

Table 6 lists the univariate intravascular ultrasound predictors of restenosis at the $P<0{\cdot}05$ level. Ultrasound variables that were not predictive at the $P<0{\cdot}05$ level included plaque composition (dominant soft vs fibrotic vs calcific plaque), calcium location and arc of superficial calcium, minimal wall thickness and dissections after intervention.

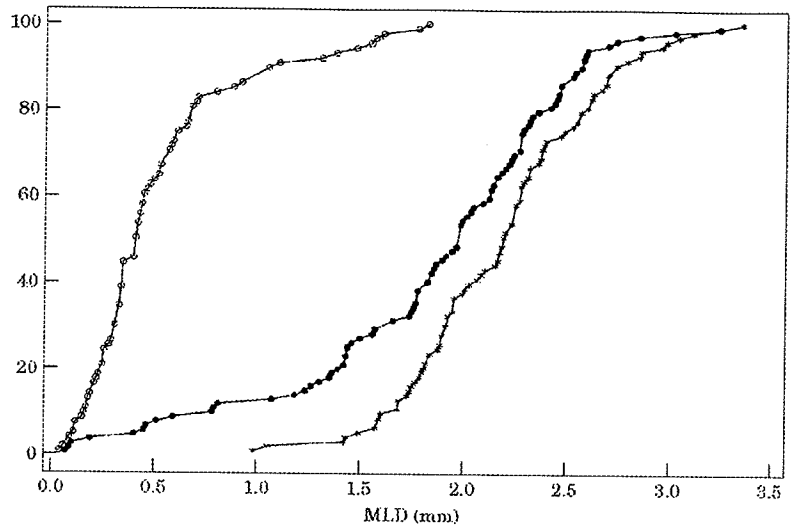

Figure 1 **Cumulative frequency distribution curves showing minimal lumen diameters measured before and after intervention and at follow-up. ○ = pre-PTCA; * = post-PTCA; ● = follow-up.**

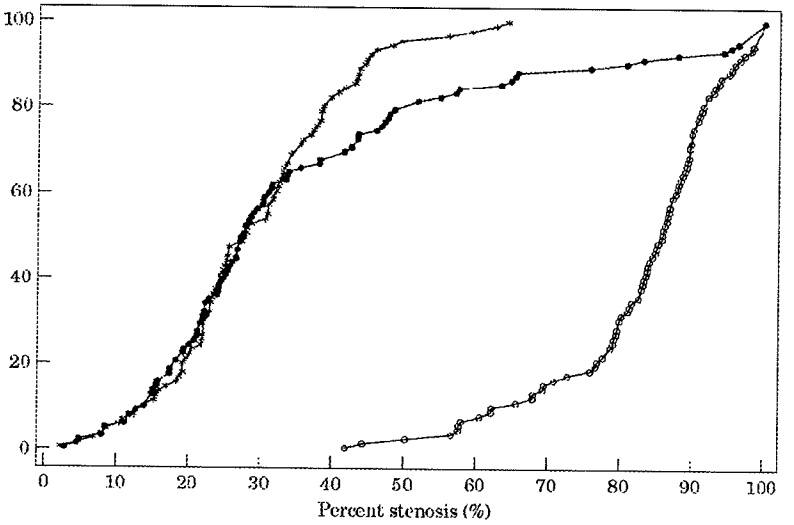

Figure 2 **Cumulative frequency distribution curves of the percentage of stenosis. Symbols as for Fig. 1.**

Long-term clinical events

All patients had a clinical follow-up after at least 12 ± 3 months following intervention. One patient died 4 weeks after PTCA following bypass surgery due to three-vessel disease. In 13 patients PTCA was performed (in 10 of these patients re-PTCA for restenosis at the target lesion site). Three patients had had a myocardial infarction (two in the perfusion area of the target vessel). The cumulative event rate (including acute and follow-up events) for the total group was 16% and for the target vessel 12% (see Fig. 3).

Discussion

The novel findings of this study are as follows: (1) the use of vessel size-adapted intravascular ultrasound

Table 2 Base line angiographic and ultrasound characteristics of the 144 patients included in the trial

Characteristic	n = 152 lesions (%)
One-vessel disease	93 (64)
Multi-vessel disease	51 (36)
Target lesion	
LAD	99 (65)
LCX	14 (9)
RCA	39 (26)
Type of lesion	
A	16 (11)
B1	46 (30)
B2	89 (59)
Average lesion length (mm)*	7·68 ± 3·59
Incidence of calcifications	93 (61)
Mild	34 (22)
Severe	59 (39)

*Plus-minus values are means ± SD; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Table 3 Serial angiographic measurements, pre PTCA, post PTCA and at follow-up

	n = 152
Reference diameter (mm)*	
Before angioplasty	2·61 ± 1·00
After angioplasty	2·81 ± 1·01
At follow-up	2·81 ± 1·01
Minimal luminal diameter (mm)	
Before angioplasty	0·50 ± 0·41
After angioplasty	2·23 ± 0·58
At follow-up	1·76 ± 0·81
Gain	1·75 ± 0·71
Late loss	0·50 ± 0·90
Net gain	1·25 ± 0·87
Stenosis (%)	
Before angioplasty	82·2 ± 12·5
After angioplasty	28·6 ± 12·9
At follow-up	36·5 ± 25·1
Gain	54·6 ± 18·8
Late loss	8·8 ± 2·1
Net gain	46·1 ± 8·1
Restenosis rate (%)**	21

*Plus-minus values are means ± SD: **Definition of restenosis according to NHLBI criterion as a follow-up diameter stenosis of >50%; PTCA = percutaneous transluminal coronary angioplasty.

guided PTCA results in the selection of larger diameter balloons; (2) this does not lead to an increased rate of acute complications; (3) angiographic success can be achieved in the majority of cases; (4) vessel-size adapted PTCA conveyed a low 1 year clinical event rate (16%) and subsequently a reduced angiographic restenosis rate (21%).

Procedural outcome

The high success rate of vessel-size adapted PTCA may be attributed to a number of factors. First, the luminal diameter achieved by angiography (2·23 ± 0·58 mm^1) and by intravascular ultrasound (5·07 ± 2·45 mm^2) prevents vessel closure despite a rather high rate of severe vessel dissections (57%). Second, the control of the procedural success, primarily by intravascular ultrasound, does not result in a higher rate of re-dilatations using higher pressures. Third, the interventions were performed by only those investigators who had extensive experience with PTCA and with intravascular ultrasound.

Table 4 Serial intravascular ultrasound measurements pre- and post PTCA

Parameter	Pre-PTCA	Post-PTCA	Gain
MLD (mm)*	1·46 ± 0·5	2·38 ± 0·81	0·92 ± 0·93
Lumen CSA (mm^2)	1·87 ± 1·3	5·07 ± 2·45	3·20 ± 2·6
EEM (mm)	4·38 ± 1·63	4·45 ± 1·18	
EEM CSA (mm^2)	14·5 ± 6·48	17·2 ± 7·4	

*Plus-minus values are means ± SD.
IVUS = intravascular ultrasound; PTCA = percutaneous transluminal coronary angioplasty: MLD = minimal lumen diameter; CSA = cross-sectional area; EEM = external elastic membrane.

Table 5 Procedural parameters of balloon angioplasty

Parameter	
Dilatations (per patient)*	1·5 ± 1
Dilatation time (s)	130 ± 60
Balloon diameter (mm)	4·0 ± 0·5
Balloon pressure (atm)	7·0 ± 2·0
Balloon/EEM ratio	0·84 ± 0·13
Balloon diameter/angiographic vessel diameter ratio	1·38 ± 0·25

*Plus-minus values are means ± SD; EEM = external elastic membrane.

Late outcome

While the reported angiographic restenosis rates (>50% diameter stenosis at follow up) have ranged from 22% to 45% for the different stents[8,9,37–40] and 13% for the heparin coated Palmaz–Schatz stent[41], the angiographic restenosis rate in this study was 21%. In our study, vessel-size adapted interventions resulted in an acute net gain of 3·4 ± 2·3 mm^2 (external elastic membrane cross-sectional area), which corresponded to a gain of 1·75 ± 0·71 mm by QCA criteria. These results compare favourably to previous trials with stents, which had an acute luminal gain ranging from 1·4 mm to 1·7 mm by QCA and a late loss at follow-up from 0·66 mm to 0·75 mm, associated with restenosis rates ranging from 22% to 32%[8,9]. In this study, acute luminal gain at the site of PTCA was 1·75 mm and late loss at follow-up was 0·5 mm, which was associated with an angiographic restenosis rate of 21%. This late low loss index of 0·28% and large net gain of 1·25 mm indicates that the policy of 'angiographic oversizing'

Table 6 Univariate IVUS predictors of restenosis

Variable	No restenosis (n=90)	Restenosis (n=22)	*P*
Reference site			
Reference diameter (mm)*	5·16 ± 0·58	5·39 ± 0·38	0·14
Reference CSA (mm^2)	21·30 ± 4·63	20·56 ± 6·18	0·49
Pre-intervention lesion site			
MLD at lesion site (mm)	1·50 ± 0·45	1·48 ± 0·49	0·74
CSA at lesion site (mm^2)	1·94 ± 1·22	1·87 ± 1·58	0·52
EEM diameter (mm)	4·62 ± 0·74	4·85 ± 0·81	0·31
EEM CSA (mm^2)	17·08 ± 5·41	19·40 ± 5·86	0·16
Post-intervention lesion site			
MLD at lesion site (mm)	2·63 ± 0·47	2·33 ± 0·25	0·02
CSA at lesion site (mm^2)	5·75 ± 2·08	4·56 ± 0·89	0·01
EEM diameter (mm)	4·91 ± 0·56	5·05 ± 0·75	0·44
EEM CSA (mm^2)	19·17 ± 4·26	20·56 ± 3·91	0·62

*Plus-minus values are means ± SD.
IVUS=intravascular ultrasound; MLD=minimal lumen diameter; CSA=cross-sectional area; EEM=external elastic membrane.

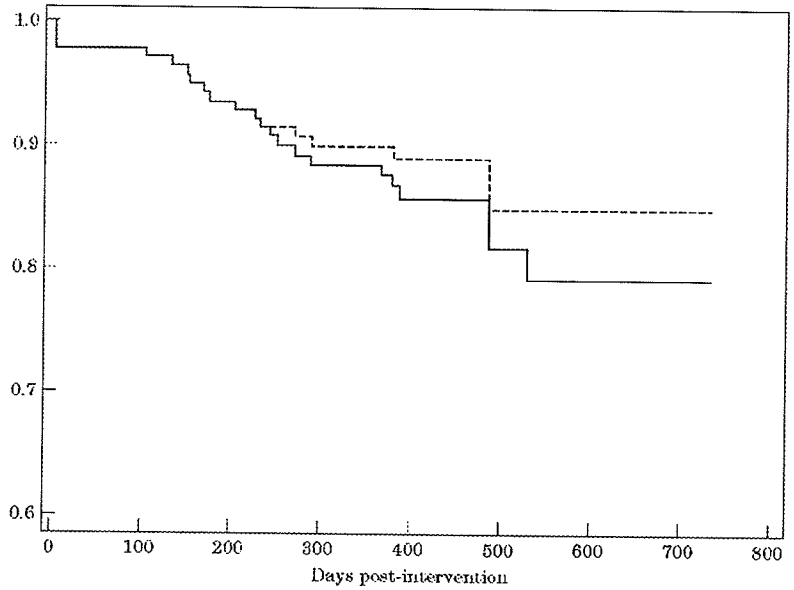

Figure 3 **Kaplan–Meier survival curves for major cardiac events (death, myocardial infarction, coronary-artery bypass surgery, and repeated angioplasty). ——=per patient; – – –=per target vessel.**

results in sufficient mechanical remodelling of the vessel, which enables accommodation of a rather low luminal loss and results subsequently in a low restenosis rate. The increased arterial distensibility resulting from dissection and 'overstretch' injury might also contribute to an improved long-term angiographic outcome using the vessel size-adapted technique, as compared with vessels treated with the conventional approach (see Fig. 4).

The clinical event rate during 1 year follow-up substantiates the favourable results of the QCA analysis. A clinical event rate of 12% per target vessel or 16% per patient compares favourably to trials using the conventional technique of PTCA and even to those trials using stent deployment to reduce restenosis rates[2,3,8,9]. When initiating this non-randomized prospective trial we decided not to limit follow-up to 6 months but rather to extend the observation period to 12 months. The obvious problem of a longer follow-up period is the reduced rate of angiographic controls, since patients will refuse an invasive re-study when free of angina pectoris. It is well known that there is a rather limited correlation between the clinical and angiographic restenosis rate. In our study, both the clinical (16%) and the angiographic (21%) restenosis rates suggest that the approach of using

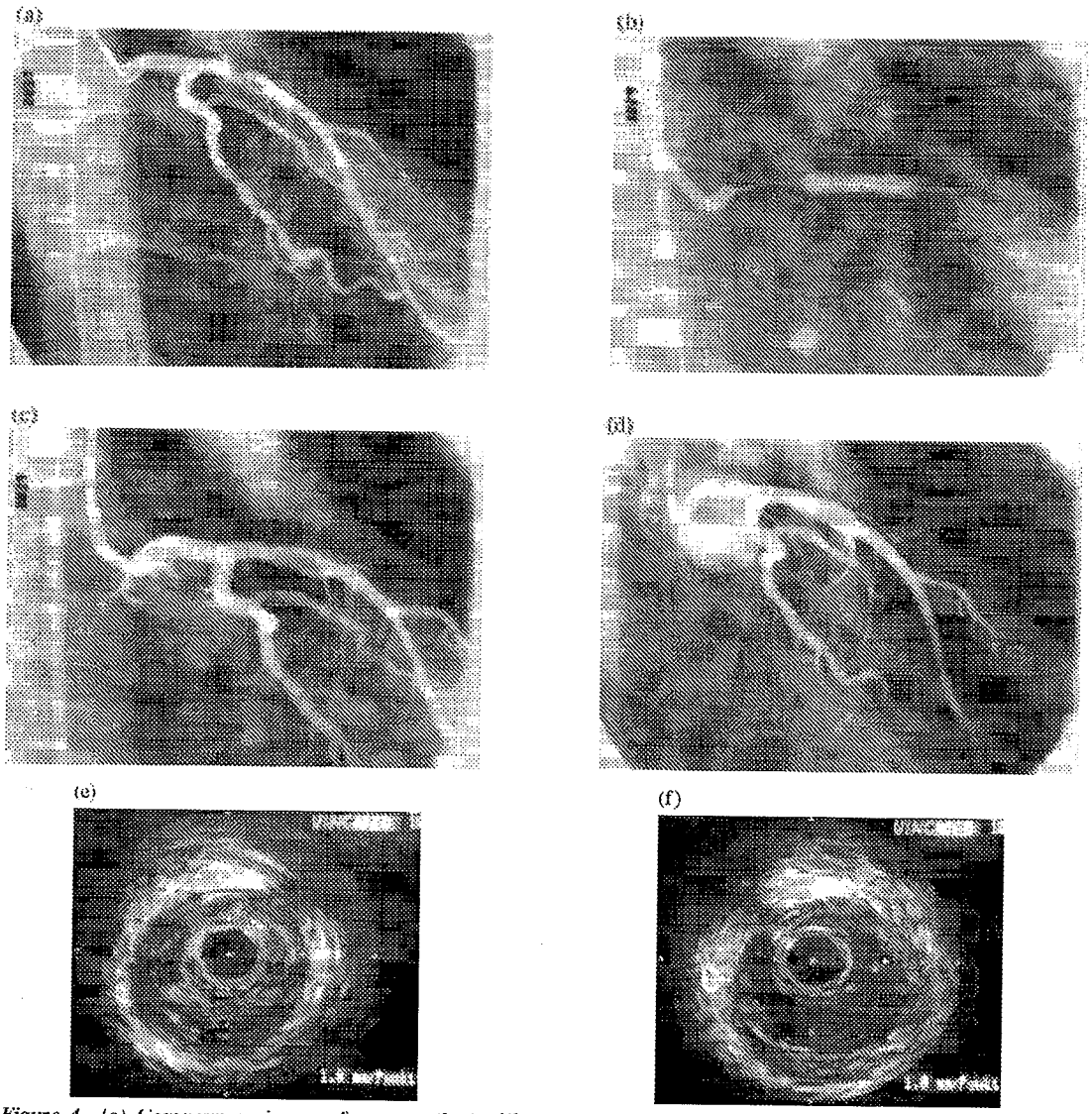

Figure 4 **(a) Coronary angiogram from a patient with a proximal left anterior descending artery stenosis before angioplasty. (b) After a 0·014 inch guidewire has been placed in the periphery of the target vessel, a 5·0 mm balloon (Schneider, Bypass Speedy) is positioned in the stenotic vessel segment and inflated with a pressure of 7 atmospheres over a time period of 120 s. (c) The result immediately post-PTCA shows a 20% residual stenosis with no visible dissection. (d) Control angiography 1 year following the intervention shows an excellent long-term result. (e) In the pre-interventional intravascular ultrasound images, the catheter was 'stuffed' into the lesion; the lesion contained almost exclusively 'soft' plaque elements (the plaque elements were less dense than the reference adventita). External elastic membrane diameter of this vessel was 5·4 mm, external elastic membrane cross-sectional area was 22·2 mm^2. (f) The post-interventional intravascular ultrasound image shows a cross-sectional area at the lumen site of 13 mm^2 indicating a sufficient luminal gain achieved by balloon angioplasty (f).**

vessel size-adapted balloon angioplasty may indeed lead to a reduction in restenotic lesions. This results from the different 'healing' effects of the vessel wall, rather than pure mechanical scaffolding, as can be achieved by stents. The promising results of this study warrant verification in larger-scale randomized trials.

Study limitations

Although this study represents a series of patients studied pre-intervention and post-intervention in whom follow-up angiography was available at a rate of 75%, it is a study of patients presenting for angiographic

follow-up largely because of symptomatic recurrence. Thus, because of the nature of the 'clinical' follow-up, it may represent a population of patients with an increased rate of restenosis, and no conclusion about the absolute restenosis rate (which was 21%) should be inferred from these data.

The results of this study were dependent on accurate identification of the same anatomical cross section on serial ultrasound studies. The lack of a motorized pull-back of the ultrasound catheter is a limitation of the study. Careful attention to lesional and peri-lesional markings, however, helped ensure identification of the same anatomical cross-section on repeated imaging. This is attested by the high reproducibility and low variability of the serial measurements.

Differences in vascular tone could have contributed to measurements of lumen dimensions. However, all patients were studied only after administration of significant doses of intracoronary nitroglycerin, and differences in vascular tone should not have affected measurements of lumen dimensions significantly.

It also had to be stated that arbitrary intravascular ultrasound end-points were used for definition of acute success. It is therefore not clear if the adoption of different end-points with selective usage of stenting for unsuccessful results would have led to a better outcome.

This study involved a rather homogeneous patient population. Restenotic lesions, bypass graft lesions, vessel diameters of less than 2·0 mm as determined by angiography, vessel occlusions, and vessels with severe angulations were excluded from this study. Intravascular ultrasound-guided PTCA was not performed in these lesions and the clinical event rate, as well as the incidence of angiographic restenosis cannot be extrapolated from the data of this study.

Clinical implications

Treatment strategies to prevent restenosis have focused on limitation of elastic recoil, platelet aggregation with release of growth factors and cellular proliferation[5–9,42]. So far, reduction in the incidence of restenosis in some focal lesions of native coronary arteries has been confined to stents. In this prospective, non-randomized trial it could be demonstrated that intravascular ultrasound-guided size-adapted PTCA also results in a reduction in the clinical event rate and the angiographic restenosis rate during a follow-up period of 1 year. The results of this study underline that 'vessel-size adapted' PTCA may be equally effective or better than treatment strategies using stents for achieving long-term success following percutaneous interventions of obstructive coronary artery disease. A large-scale randomized trial is warranted to verify the results of this trial.

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Verapamil—A Cardioprotective Strategy

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Prevention of Restenosis After PTCA: Role of Calcium Antagonists

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Summary: The recurrence of coronary obstruction after initially successful percutaneous transluminal coronary angioplasty (PTCA) represents a major problem of this interventional procedure at present. In the pathogenesis of restenosis the growth factor–dependent proliferation and migration of medial smooth muscle cells into the intima of the vessel wall may play a very important role. In experimental studies this process could be inhibited by calcium antagonists. However, the first two placebo-controlled clinical trials showed disappointing results: the restenosis rate was not decreased by the treatment with 10 mg of nifedipine four times daily or by the treatment with 90 mg of diltiazem three times daily. The influence of high-dose verapamil treatment [Isoptin RR (240 mg) twice daily] on the recurrence of coronary stenosis has been investigated by a recently completed double-blind, placebo-controlled trial, the verapamil angioplasty study (VAS). The VAS included 196 consecutive patients with at least one risk factor for restenosis after successful PTCA for stable angina pectoris ($n = 75$) or unstable angina pectoris/non–Q-wave infarction ($n = 97$). Eighty-eight percent of the patients underwent follow-up angiography at 4.3 ± 2.3 months. The publication of detailed data of the VAS including restenosis rates in both clinical subgroups is being prepared.
Key Words: Calcium-channel blockers—Coronary angioplasty—Prevention of restenosis.

Within the last decade percutaneous transluminal coronary angioplasty (PTCA) has gained increased acceptance as an effective treatment for selected patients with coronary artery disease. Due to the growing experience of the operators and to technical developments of the catheters, the primary success rate of the procedure has been increased from 64% (1) to over 90% in experienced laboratories (2). The long-term benefit of PTCA, however, is limited by the recurrence of coronary obstruction in a substantial subset of patients (3–11). The efficacy of various adjunctive treatments for decreasing restenosis rates after PTCA has been investigated (9,10,12–19). The results of these trials were contradictory or negative. Thus, at present no generally accepted medical management for patients following successful PTCA exists.

PATHOGENESIS OF RESTENOSIS

The reduction in coronary obstruction by PTCA is achieved by splitting the intima and media (20,21) and stretching the medial layer. This injury to the vessel wall is responded to by a repair process that may or may not result in a recurrent stenosis. At present, different mechanisms are believed to be involved in the development of restenosis (22). Although many details of the complex reactions are not fully understood, recent results of morphologic investigations and experimental studies suggest a certain sequence of events following PTCA (23,24): early, i.e., within 30 min after injury to the arterial wall, platelets adhere to the irregular subendothelial surface. Platelet aggregation and local thrombus formation follow, but according to autopsy studies thrombus formation seems to be of minor importance for the development of restenosis. Platelet-derived growth factor (PDGF) and other proteins with similar or supplementary effects are secreted from the α-granules of the adhering platelets. The PDGF is not only released into the circulation where it is rapidly inactivated, but it also enters the vessel wall and reaches the medial layer. Here, PDGF is assumed to initiate intimal hyperplasia by stimulating the change of the phenotype of smooth muscle cells (SMCs) from a contractile to a synthetic mode and by stimulating the migration of medial SMCs into the intima. The PDGF pool of the media does not only derive from adherent

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platelets but also from damaged endothelial cells, directly injured SMCs, and macrophages.

Whether development of restenosis occurs may depend on the number of activated medial SMCs, which is modulated by the inhibitory effect of intact endothelial cells on the one hand and by the activating effect of direct injury and of mitogenic factors such as PDGF on the other hand. In addition, regional flow characteristics may influence the recurrence of coronary stenosis, as an inverse relationship between the level of wall shear stress and the extent of intimal thickness has been reported (23).

This hypothetical model of the development of restenosis after angioplasty is supported by a variety of clinical findings: the peak incidence of restenosis occurs 2–4 months after the procedure (11,25), when SMC proliferation and the synthesis of connective tissue are completed. A later development of restenosis at the same site is very unlikely (26).

Several predictors of restenosis can be related to special blood flow characteristics (24): the high blood flow velocity in proximal vessel segments and in the left anterior descending coronary artery can cause greater neointimal hyperplasia because of greater areas of fluid separation. Higher restenosis rates of eccentric lesions (27,28) and of residual obstructions of more than 30% (6) could be due to the persisting low shear stress conditions in the immediate poststenotic segment (24). The high extent of injury to medial SMCs may cause the high restenosis rates of pre-PTCA obstructions > 90% (3,6,24). The amount of delivered mitogenic platelet-derived factors depends on the area of a direct contact between subendothelial tissue and adhering platelets. The size of this contact area increases with increasing length of the obstruction; this may explain the finding of high restenosis rates in long obstructions (29).

RATIONALE FOR TREATMENT WITH CALCIUM-CHANNEL BLOCKERS AFTER PTCA

Several studies have shown an antiatherosclerotic effect of different calcium antagonists in hypercholesterolemic rats, rabbits, or monkeys (30–33). In addition, in normocholesterolemic animals with localized arterial injury calcium antagonists were found to exhibit antiproliferative effects (34,35). Some possible mechanisms may be derived from the results of recent cell culture experiments with vascular SMCs (36,37). According to these studies, the beneficial effect of calcium antagonists appears to be related to the inhibition of cholesteryl ester accumulation by calcium antagonists in the presence of hypercholesterolemic plasma (30,36). In the absence of hypercholesterolemic conditions, PDGF-stimulated actions such as the activation of protein kinase C, the rise in the cytoplasmic concentration of free calcium, and vasoconstriction could be inhibited by calcium antagonists (37). By use of ^{3}H-thymidine, a concentration-dependent inhibitory effect of calcium-channel blockers on the mitogenic action of PDGF was observed (37–39).

Only recently, two controlled clinical trials on the influence of calcium-channel blockers on the progression of coronary artery disease were published. Neither nifedipine (40) nor nicardipine (41) showed any influence on the progression or regression of preexisting coronary lesions of more than 20% over a time interval of 3 and 2 years, respectively. However, the progression of minimal lesions of 5–20% was significantly suppressed by nicardipine (41). The INTACT study (40) showed a reduction in the development of new coronary lesions by the medication with nifedipine, whereas preexisting obstructions were not significantly influenced. Since in this study only narrowings of ≥20% were accepted as stenoses, the results of the INTACT and the nicardipine trial are not contradictory. They seem to confirm experimental data suggesting that any beneficial effect on human atherosclerosis is most likely to be obtained for the early events of proliferative lesion formation (42).

The results of both the experimental studies and the clinical trials refer to the relatively slow process of spontaneous atherosclerosis. It seems reasonable to test the hypothesis that the accelerated response to the vascular injury, which is provoked by coronary angioplasty, can be slowed down by calcium-channel blockers.

CLINICAL TRIALS WITH CALCIUM-CHANNEL BLOCKERS FOR THE PREVENTION OF RESTENOSIS AFTER PTCA

The first two placebo-controlled trials led to disappointing results. Corcos and colleagues (10) included 92 patients who underwent primary successful PTCA. The patients were randomly assigned either to receive diltiazem, 90 mg three times daily for 3 months (n = 46), or to receive a placebo three times daily (n = 46) in addition to the baseline medication with platelet inhibitors. After 8 ± 5 months, the follow-up angiogram revealed a slight increase in the degree of stenosis from 38 ± 25% immediately after PTCA to 42 ± 23% in the diltiazem group. In the control group, the mean degree of obstruction increased from 37 ± 12% immediately after PTCA to 44 ± 23% after an identical observation period. In the diltiazem group the restenosis rate was 15%, which was not significantly different from that of 22% in the placebo group.

In 1986 Whitworth and co-workers (9) reported a randomized, placebo-controlled study about the influence of nifedipine, 10 mg given orally four times daily, on the restenosis rate after PTCA. Two hundred forty-one patients were enrolled, and 82% were restudied angiographically at 6.5 ± 2 months (nifedipine group) and at 6.6 ± 3 months (placebo group) after PTCA. The mean diameter of stenosis immediately after PTCA was 23 ± 11% in the nifedipine group and 23 ± 10% in the placebo group. At restudy, the mean ob-

struction increased to 36 ± 23% in the nifedipine group and to 37 ± 23% in the control group. The calculation of restenosis rates gave similar results in both groups (28 vs. 29.5%, NS). The authors concluded that in the absence of clinically apparent coronary artery spasm (such patients were excluded from the trial), routine therapy with calcium antagonists after PTCA is no longer justified.

Both trials showed specific, possibly crucial problems of the study design: in the diltiazem trial a reduction in restenosis rate by one third did not reach significance level. As only 92 patients were enrolled, it may be speculated that the negative result could stem from the rather small sample size. In the nifedipine trial, the relatively low dose of 40 mg of nifedipine daily may have concealed a possible beneficial effect. Because the results of these two studies did not appear conclusive, we started in 1987 a double-blind, placebo-controlled clinical trial in patients after PTCA receiving a high dose of verapamil. To improve the sensitivity of the study design, only patients with a high risk of restenosis were selected.

THE VERAPAMIL ANGIOPLASTY STUDY (VAS): STUDY DESIGN AND PATIENT RECRUITMENT

Two subgroups of patients with successful PTCA were assigned separately to either the treatment group or the placebo group: patients with chronic stable angina and patients with either unstable angina or non-Q-wave infarction. The study protocol included two outpatient examinations at 2 and 4 months after PTCA. At these two occasions, the patient's history was taken and an electrocardiogram and a pill count were obtained. The same procedures were performed at 6 months after entry to the study in addition to follow-up coronary angiography. The study protocol allowed earlier follow-up angiography, if recurrence of stenosis was suspected.

Consecutive patients were eligible who underwent successful PTCA at our institution from April 1987 through March 1989. For entering the trial, patients had to have at least one of the following risk factors for restenosis: diabetes mellitus, multivessel coronary artery disease, total or subtotal occlusion of the dilated segment, eccentric lesion, proximal stenosis of the left anterior descending coronary artery, and/or post-PTCA stenosis ≥ 30%. Exclusion criteria consisted of acute transmural infarction, congestive heart failure, age > 70 years, pregnancy, history of coronary bypass surgery, prior PTCA of the same segment, severe renal or hepatic failure, bradycardia < 50 beats/min, sick sinus syndrome, second- or third-degree atrioventricular block, persistent medication with calcium antagonist or beta-blocker after PTCA, and/or lack of informed consent of the patient.

Throughout the recruitment period 1,325 PTCA procedures were performed in 1,076 patients. The inclusion criteria of the study protocol were met by 196 patients (18%). The basis medication after PTCA consisted of dipyridamole 75 mg plus aspirin 330 mg twice daily. The 196 patients were randomly assigned either to the treatment with 240 mg of verapamil ($n = 98$) or with a placebo ($n = 98$) both given orally twice daily. The proportion of patients with stable angina pectoris was 42% in the treatment group and 43% in the placebo group. Both patient groups did not differ significantly with regard to age, sex, or distribution of risk factors for recurrent stenosis (Table 1).

TABLE 1. *Distribution of age, sex, and risk factors for restenosis after PTCA in the 98 patients of the verapamil group and the 98 patients of the placebo group*

Variable	Verapamil ($n = 98$)	Placebo ($n = 98$)	p
Age (years)	55 ± 8	55 ± 7	NS
Male (%)	79	85	NS
Diabetes mellitus (%)	14	4	NS
Multivessel disease (%)	36	42	NS
Proximal lesion of the left anterior descending coronary artery (%)	61	67	NS
Eccentric narrowing (%)	58	47	NS
(Sub)total occlusion (%)	12	13	NS
Post-PTCA lesion ≥30% (%)	66	68	NS

PTCA, percutaneous transluminal coronary angioplasty.

Follow-up angiography was refused by nine patients of the verapamil group and by 15 patients of the placebo group. These 24 patients (12%) were excluded from further analysis because the restenosis rate could not be adequately evaluated. The results of the remaining 172 patients were analyzed on an intention-to-treat basis. Films were evaluated by two independent experts blinded to the identity of the patients. The quantitative assessment of coronary obstruction was based on edge tracings measured by electronic calipers. Restenosis was defined as a loss of at least 50% of the initial gain in stenotic diameter.

Restenosis rates of VAS were presented at the American Heart Association meeting in 1990 (43). Detailed data are being prepared for publication.

The design of the VAS showed important differences from the designs of the two other calcium channel blocker trials mentioned before: a rather high dose of the calcium antagonist was used, as experimental data suggested an antiproliferative effect of calcium blockers to be achieved only at high plasma concentrations. Second, by the selection of patients with high risk for recurrent stenosis, even the smaller number of patients that had to be enrolled into the study could yield a positive result, due to higher event rates. Third, the separate randomization of patients with chronic and acute coronary syndromes allowed for identifying possible separate effects of verapamil on the restenosis rates in patients with stable angina pectoris on the one hand and in patients with unstable angina/non-Q-wave in-

farction on the other hand. Finally, according to the results of cell culture experiments the calcium antagonist verapamil may be more potent in inhibiting the proliferation of SMCs as compared to nifedipine or diltiazem (37).

CONCLUSION

Experimental data provide sufficient evidence for an antiproliferative effect of calcium antagonists. This effect appears to be considerably due to the inhibition of actions mediated by PDGF and other proteins with similar mitogenic properties. The development of restenosis after PTCA can be assumed to be related to the activation of these growth factors. The disappointing results of early clinical trials using diltiazem or nifedipine for treatment after PTCA may be influenced by the study design. The effect of high-dose verapamil treatment on restenosis rates in patients with stable angina pectoris and in patients with unstable angina has been investigated separately in the recently completed VAS.

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